Peritoneal metastases of colorectal origin—cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). The financial aspect

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ABSTRACT:
About 10% to 15% of patients with colon cancer have intraperitoneal metastases at diagnosis. The patients with intraperitoneal metastases and without distant metastases can benefit from cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Because up to a half of patients live for at least 5 years after this treatment, the treatment is used more and more often. The treatment of patients with intraperitoneal metastases with CRS and HIPEC costs more than the majority of other medical procedures, because CRS is extensive and takes a lot of time, and after surgery, patients need intensive care and expensive medications and equipment. Currently, only 40% to 80% of costs of CRS and HIPEC are reimbursed in Poland. Because CRS and HIPEC mean a financial loss to hospitals, they are rarely performed. We analyzed the costs of treating patients with peritoneal metastases by CRS and HIPEC in two centers (Gdansk, Wroclaw) and showed how this treatment is reimbursed outside Poland. We discussed whether adequate qualification of patients and experience of the teams giving the treatment could reduce the costs.

KEYWORDS: metastases to the peritoneum, HIPEC, medical costs.

INTRODUCTION
In approximately 10-15% of patients suffering from colorectal cancer, peritoneal carcinomatosis is also observed at the time of diagnosis. Even larger percentage of metastases to peritoneum is observed in case of local recurrence of this neoplasm, reaching 40%. With yearly morbidity due to cancer of colon and intraperitoneal part of rectum reaching 15.000 in Poland, the number of patients with peritoneal carcinomatosis is very high.

Prognosis in untreated, or treated only symptomatically, disseminated peritoneal carcinomatosis is negative. Mean survival is 6-12 months.

In early stages, when metastases of colorectal cancer to peritoneum are limited and there is no evidence of metastasis occurring via blood, effective treatment is possible allowing to reach 5-year survival of around 50%. This is comparable to the outcome of surgical treatment of liver metastases of colorectal cancer.

Achieving such impressive results of patients with peritoneal carcinomatosis of colorectal cancer is dependent on many factors. The most important one is stage, determined using PCI (Peritoneal Cancer Index) scale to be no more than 20 pts., and possibility to conduct CRS – complete macroscopic cytoreduction (CC-0) in conjunction with Hyperthermic Intrapерitoneal Chemotherapy (HIPEC).

Results of treating patients with metastases to peritoneum have encouraged many centers, including some in Poland, to increasingly widely use this method of treatment. Multiple factors affecting patient outcomes were analyzed, including appropriate eligibility determination, diagnostics, adjuvant therapy eligibility determination procedure, and treatment cost. The latter are high with respect to single procedure cost, but relatively low when viewed in the light of achieved results and total expenditure per therapy.

Active treatment of peritoneal carcinomatosis of colorectal cancer is recommended in guidelines by National Consultant in the field of oncologic surgery (1) as well as national guidelines in many other countries (2, 3). Recently published ESMO guidelines recommend this treatment protocol indicating that due to outcomes achieved after CRS+HIPEC it is planned to recognize it as standard of care (4).

COST OF SURGICAL TREATMENT OF PATIENTS WITH PERITONEAL CARCINOMA
Expenditure for treatment of patients operated on at the Clinic of Oncologic Surgery of UCC in Gdańsk and Clinic of Oncologic Surgery of Lower Silesian Centre of Oncology in Wroclaw was analyzed. Financial data were obtained from respective financial departments of hospitals. Ten subsequent cases operated on at each clinic were taken into account which was a representative sample for cost of treatment analysis.

In order to compare respective cost components of procedure and indirect cost, single-use equipment, drugs, laboratory diagnostics, non-preoperative diagnostics, operating suite, anaesthesia services, personnel (including operator and assistant fees) and hospital ward costs were all taken into account. The results of cost analysis are presented in Table I.

Insurance payment for treatment of peritoneal carcinomatosis of colorectal cancer is currently based on type of procedure, without taking into account the scope of organ and peritoneum resection. For example, the fee paid for partial colon resection, lasting 1.5 – 2
hours, is exactly the same as for radical resection of metastases of colorectal cancer which includes partial resection of colon/rectum, partial resection of small intestine, stripping of parietal peritoneum, cholecystectomy, splenectomy, liver capsule stripping which lasts approximately 6-8 hours. The cost of the procedure is increased due to longer duration of anaesthesia, operating suite and ICU costs, required for patients undergoing such broad and long operations.

Average total cost of hospital treatment is 14 650 PLN. Insurance payment for surgical procedures is insufficient to cover this in full, and varies between 41% and 81% of actual expenditure. Insurance payments for different procedures are detailed in Table II.

**COST OF SURGICAL TREATMENT OF PERITONEAL CARCINOMATOSIS OF COLORECTAL CANCER – LITERATURE DATA**

Treatment of peritoneal carcinomatosis without metastasis outside of peritoneum (i.e. via blood) using cytoreductive surgery accompanied by hyperthermic intraperitoneal chemotherapy is performed increasingly widely. This might be caused in part by replicability of outcomes of patients treated at many different centers. Increasing acceptance of this method, leading in the direction of setting it as treatment standard in some clinical situations (4), despite low number of randomized studies, caused increased interest in cytoreductive surgery and HIPEC. During the last decade, a number of published studies concerning this method has quintupled. One of the often mentioned aspects is financial matters. Unfortunately, the number of published studies in this matter is low, and in Poland, this work is the first one to estimate financial cost of treatment of patients with peritoneal carcinomatosis. This is especially important in environments where insurance payments are lump sums, often calculated below actual costs. CRS and HIPEC might be accounted for under existing procedure categories, despite actual cost being higher than the lump sum payment due to objective factors.

In studies published worldwide, treatment cost issues are often described in the context of not only the patient’s outcome, but also cost of diagnostics, eligibility determination and disease stage.

One of the components directly increasing the treatment cost is ICU stay. A study by Mogal et al. published in 2016 (5) mentions among others the cost of such a stay of patients who had undergone cytoreductive surgery with HIPEC. A group of 1064 patients was evaluated, including 224 (23%) who were moved directly to surgical ward after surgery. Remaining 840 patients were treated at ICU post-operatively. The analysis took into account demographic data, site of primary tumor, comorbidities, blood loss, extent of cytoreductive surgery, ECOG score and survival rate.

Eligibility determination for post-operative ICU stay according to site of primary tumor is presented in Table III.

No statistically significant difference between number of patients qualified for ICU stay between different categories of cancer was observed (p=0.077). Percentages of patients not requiring an ICU stay varied between 17% and 35% (mean: 23%). Univariate analysis has shown correlation between pre-operative albumin level to the frequency of positive eligibility determination for ICU stay (p<0.0001). Multivariate analysis has not confirmed this result (p=0.183), however authors recommend in conclusion to take nutritional status into account when qualifying for post-operative care site. BMI was not statistically significant in uni- and multivariate analysis (p=0.7535 and p=0.3716, respectively).

Analysis of survival duration post CRS+HIPEC procedure has shown a better outcome in patients not requiring ICU stay or when such a stay was shorter than 48 hours. Average survival was 5.4 and 2.12 years, respectively. A 3- and 5-year survival was 67%
plasm and clinical signs and symptoms.

Appropriate eligibility determination in the last 3 years (study published in 2013) has resulted in 35% of patients not requiring routine post-operative care at ICU, compared to 19% previously. However, the authors do not recommend routinely moving patients to surgical wards instead of ICU post-operatively using presented criteria in centers without extensive experience in CRS + HIPEC procedures (5).

Authors of another study concerning cost analysis of patients with peritoneal carcinomatosis came to a similar conclusion. Vanonu-onu et al. (7) emphasize lower number of post-operative complications, lower amount of blood given, lower time to discharge, shorter stay at ICU with increasing experience of the operating team. Learning curve for CRS+HIPEC is comparable to learning curve for Whipple procedure, in which increased experience results in complications and post-operative mortality falling. Cytoreductive surgery in cases of peritoneal carcinomatosis is connected with a wide range of organ resections. In studies evaluating QoL, a decrease in quality of life was observed after the operation, which gradually returned to pre-operative values during the period of 1 year. According to studies evaluating QoL, CRS+HIPEC should not be disregarded on the basis of QoL outcome. In the aspect of pre-operative eligibility evaluation for CRS+HIPEC, improved time to discharge, operating suite and ICU cost as well as cost of equipment used should be taken into account.

In conclusion, the authors remark that there is no data justifying routine stay at ICU for patients undergoing CRS +HIPEC, as it generates extra costs and limits availability. In the US, ICU costs increase procedure expenses by 20%. Generally, ICU stay increases the cost of hospital stay by 2.5 times.

Taking into account differences in survival of patients connected with general condition and ICU stay necessity connected with it, appropriate eligibility determination of patients for treatment is imperative, with taking the hospital stay costs into account. To achieve such a goal, PSDSS classification appears very useful, as it includes not only stage of peritoneal carcinomatosis using PCI (Peritoneal Cancer Index), but also histological grade of the neo-

Tab. II. Insurance payments for different partial procedures.

<table>
<thead>
<tr>
<th>SURGICAL PROCEDURE</th>
<th>AVERAGE INSURANCE PAYMENT (PLN)</th>
<th>% OF ACTUAL COSTS (X/14 650 PLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial large intestine resection</td>
<td>11 600</td>
<td>79%</td>
</tr>
<tr>
<td>Laparotomy + peritoneal stripping</td>
<td>6000</td>
<td>41%</td>
</tr>
<tr>
<td>Laparotomy + splenectomy</td>
<td>6000</td>
<td>41%</td>
</tr>
<tr>
<td>Laparotomy + cholecystectomy</td>
<td>1550</td>
<td>10.5%</td>
</tr>
<tr>
<td>Laparotomy + gastrectomy</td>
<td>11 800</td>
<td>80.5%</td>
</tr>
<tr>
<td>Laparotomy + omentectomy</td>
<td>6000</td>
<td>41%</td>
</tr>
<tr>
<td>Laparotomy + partial cystectomy</td>
<td>6000</td>
<td>41%</td>
</tr>
<tr>
<td>Laparotomy + partial ileo-/jejunoectomy</td>
<td>7120</td>
<td>48.6%</td>
</tr>
<tr>
<td>Laparotomy + partial colectomy + partial ileo-/jejunoectomy + cholecystectomy + splenectomy + partial upper proctectomy + partial cystectomy + omentectomy + liver capsule stripping + parietal peritoneum stripping + ovarianectomy + hysterectomy</td>
<td>11 600</td>
<td>79%</td>
</tr>
</tbody>
</table>

Tab. III. Eligibility determination for post-operative ICU stay according to the site of primary tumor.

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>NUMBER OF PATIENTS STAYING IN SURGICAL WARD/IN ICU</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>45/184</td>
<td>20/80</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>14/67</td>
<td>17/83</td>
</tr>
<tr>
<td>Ovary cancer</td>
<td>28/52</td>
<td>35/65</td>
</tr>
<tr>
<td>Appendix cancer</td>
<td>128/409</td>
<td>24/76</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>7/26</td>
<td>21/79</td>
</tr>
<tr>
<td>Other</td>
<td>22/82</td>
<td>21/79</td>
</tr>
</tbody>
</table>

and 49%, and 52% and 43% respectively. The difference was especially visible in patients with colorectal cancer (p=0.0386), ovarian cancer (p=0.0054) and appendix cancer (p<0.0001).

In patients qualified for post-operative stay at ICU worse outcome was observed in smokers, patients with ECOG>2, colorectal cancer, stomach cancer, ovarian cancer and in patients with level IV complication according to Clavien-Dindo scale.

Twelve out of 244 patients who were directly moved to a surgical ward post-operatively required secondary stay at ICU due to edema, respiratory or cardiac complications, perforation and bleeding. Out of 12 patients, 2 have died due to complications.

Patients treated with cisplatin during HIPEC (mainly suffering from mesothelioma) were routinely moved to ICU to assure renal function monitoring and appropriate hydration.

In conclusion, the authors remark that there is no data justifying routine stay at ICU for patients undergoing CRS +HIPEC, as it generates extra costs and limits availability. In the US, ICU costs increase procedure expenses by 20%. Generally, ICU stay increases the cost of hospital stay by 2.5 times.

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Hinkle et al. (8) underline high cost of operating suite and anesthesia, which in their data amount to 45% of the total. Cost of ward stay and drugs was 19% of total cost. Treatment total cost
was comparable to pancreateoduodenectomy or liver lobe resection and amounted to 25,917 USD. Authors state that in centers without significant experience in treating peritoneal carcinomatosis, selective eligibility determination is one way to limit costs of CRS + HIPEC procedure.

Chuia et al. (9) evaluated costs of treating peritoneal carcinomatosis depending on the primary tumor type. The study recruited 136 patients, among whom 159 CRS+HIPEC procedures were performed between 2002 and 2008. Treatment outcome was evaluated using survival rates.

Mean cost of CRS+HIPEC depending on primary tumor:

- Appendix cancer: 88,423 AUD (23,933 – 299,145)
- Colorectal cancer: 66,148 AUD (26,079 – 409,666)
- Pseudomyxoma peritonei: 92,308 AUD (11,562 – 501,144)
- Mesothelioma peritonei: 55,062 AUD (23,261 – 94,104)
- Other: 44,668 AUD (31,592 – 70,026)

Concluding, the authors state that comprehensive treatment of peritoneal carcinomatosis significantly increases treatment cost but also improves outcomes in this hard-to-treat disease. For this reason, this costs may be considered justified.

Naffouje et al. (10) also observed that CRS with HIPEC attracted interest from surgeons due to significantly better outcome and its replicability in different centers when treating peritoneal carcinomatosis. However, CRS+HIPEC procedure was not properly evaluated in the US, where different plans of medical insurance exist. In a study authored by Chicago Medical Center surgeons an analysis of hospital and surgeon’s costs and insurance payments for publicly-funded, but not teaching, hospitals was presented. Only patients treated between 06.2013 and 08.2014 were taken into account. A total of 25 patients underwent CRS+HIPEC. Twelve were privately insured (A), 13 had public health coverage. Mean procedure fee was 38,369 USD, and for A and B 37,093 USD and 39,463 USD, respectively (p=0.67). Average hospitalization duration for A was 10 days, and for group B – 11 days. Insurance payment from private and public sources was similar for A and B: 48,954 USD and 42,062 USD, respectively (p=0.53; mean for the whole sample: 45,243 USD). Average co-payment by the patient was 8,126 USD (A: 9,234 USD, B: 7,176 USD). Mean profit for the surgeon was 29,139 USD (A: 37,093 USD, B: 29,737 USD, p=0.80). Even though the sample is relatively small, the authors conclude that CRS + HIPEC procedure is profitable for both the surgeon and the hospital.

Another study, also from the US, authored by Squires et al. (11). Despite increasingly wide implementation of CRS with HIPEC, a relatively small amount of data on financial consequences of this method is published. Authors have taken into account hospital cost, insurance payment grouped by insurance type and post-operative complications between 2009 and 2013. CRS + HIPEC was performed in 64 patients, average PCI score: 19 pts, mean duration of surgery: 550 minutes. Forty patients had peritoneal carcinomatosis of appendix cancer (62%), 16 (25%) – colorectal cancer, 5 (8%) - goblet cell neuroendocrine tumor, 3 (5%) – mesothelioma. Complications arose in 42 patients (66%), including 13 (20%) of level III/IV according to Clavien-Dindo scale. Forty-two patients had private health coverage, while 22 were covered under Medicare/Medicaid. Average hospital cost was 49,248 USD. Insurance pay-ment amounted to 63,771 USD, resulting in mean profit of 14,523 USD per patient. Private coverage paid a larger sum per patient (80,747 USD) compared to public coverage’s 30,717 USD that compared to average hospital cost resulted in net loss of 17,342 USD, with only 62% of costs paid for. Overall profit from performing the procedure was only due to private health coverage.

Authors conclude that the main cost-related problem of the procedure is complications requiring hospitalization. Therefore, focus of further research should be reducing treatment cost and reducing frequency and severity of complications. Authors observed a large increase in the number of CRS+HIPEC procedures performed and increase in number of centers performing it, which causes further interest in costs associated with the procedure.

Squires reports that average hospitalization time was 13 days, including 2 days at ICU, while mean duration of the surgery was 550 minutes. PCI score was on average 19 pts with the range of 5-38 pts, which indicates optimistic outlook of the authors on possibility of achieving a good outcome in advanced stages of peritoneal carcinomatosis. Most common complications were infection (30%) and need for blood transfusion (19%). Level I/II complications did not increase the cost of treatment, but level III/IV increased the cost by 59,879 – 79,698 USD.

In a study on the costs of CRS with HIPEC procedure in a Greek center, as reported by Tentes et al. (12) 108 CRS+HIPEC surgeries performed on 105 patients between 2006 and 2011 were evaluated. The cost summary included daily hospital fee, ICU costs, materials and medicines cost, and pre-, intra- and postoperative diagnostics. Mean duration of hospital stay was 23 days, while ICU stay was 5 days. Complications were observed in 48.1 % while death occurred in 5.6 %. Average cost of the procedure was 15,677 EUR (range: 4258 – 95,990 EUR). Authors report that factors causing the increase in costs were complications (p=0.009) and long stay at ICU (p<0.001).

In Greece, procedure costs did not include: surgical suite costs, team salaries, depreciation/amortisation of equipment, blood preparations cost. Therefore, actual cost of procedure was higher than presented.

In an Italian study authored by Bagnoli et al. (13), authors remarked that treating peritoneal carcinomatosis was challenging for hospitals not only due to complexities of treatment, but also due to costs. Insurance payment for CRS+HIPEC depending on diagnosis and not procedure costs, as in Italy and other countries using that system, is often undervalued.

Authors have analysed expenditure for treating 24 patients between 09.2010 and 05.2013, focusing on operating suite expenses, ICU and hospital stay duration and health coverage payment for the procedure. Total cost included all cost-generating aspects of treatment. Procedure expenses increased with hospital stay duration, increased cost of medicines and materials and operating suite costs.

Average hospital stay was 14 days, ICU stay 2.4 days, mean duration of operating room was 585 minutes. Mean total cost of treatment was 21,744 EUR. Average coverage payment was 8,375 EUR (38.5 % of actual costs).
CONCLUSION

Treating patients with isolated peritoneal carcinomatosis using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is increasingly widely used and is likely to become a standard of care (A4). Reason for the increased attention to this procedure is the outcomes of patients who usually were directed to palliative care where survival rarely exceeds 9-12 months, whereas a radical surgical treatment with hipec allowed for 5-year survival in up to 50% of patients treated.

Surgical treatment of peritoneal carcinomatosis requires a wide range of organ resections and stripping of peritoneum. Average duration of the procedure is 6-8 hours, and the patient requires stay at intensive care unit. This collectively increases the total treatment cost in the reality of insurance payment only covering a part of it. Percentage of CRS+HIPEC costs covered varies, depending on differently valued organ resections, in the range of 41% - 81% of total.

Factors affecting treatment costs other than the scope of the surgery and its duration, are expenses for anaesthesia and ICU stay, total duration of hospitalization and occurrence of serious level III and IV complications. In order to reduce costs, appropriate eligibility determination is needed, with peritoneal carcinomatosis stage taken into account as it directly affects the treatment outcome. Level of experience of the given center is extremely important in this procedure, which influences predicted complications and appropriate eligibility determination for post-operative care at ICU. With greater experience, a larger proportion of patients may be moved straight to the surgical ward after surgery.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, as a highly specialist medical procedure, should be evaluated on its merits such us long-term advantages for patients and appropriately valued for the purpose of insurance payment. Currently, it is not viewed positively by hospital managers as it is loss-making. On the other hand, outcomes after CRS+HIPEC procedure justify its wider adoption when compared to palliative care outcomes.

As a procedure recommended in National Consultant for oncol-

logic surgery and ESMO guidelines, its appropriate valuation and insurance payments covering the full average costs are vital.

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